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(21) International Application Number: PCT/GB00/01775 (22) International Filing Date: 9 May 2000 (09.05.00) (30) Priority Data: 9911017.3 13 May 1999 (13.05.99) GB (71) Applicant (for all designated States except US): AS-TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): RUMSEY, William, Leroy [US/US]; 1800 Concord Pike, Wilmington, DE 19850 (US). FURR, Barrington, John, Albert [GB/GB]; Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (74) Agent: PHILLIPS, Neil, Godfrey, Alasdair; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PHARMACEUTICAL COMBINATION OF NEUROKININ RECEPTOR ANTAGONIST AND PROTON PUMP INHIBITOR			
(57) Abstract  A combination comprising an NK-1 antagonist and an agent capable of reducing the pH of gastric juice in the gut, and pharmaceutical compositions containing the combination, and methods of using the combination for treating various diseases.			

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## PHARMACEUTICAL COMBINATION OF NEUROKININ RECEPTOR ANTAGONIST AND PROTON PUMP INHIBITOR

**Field of the Invention**

The present invention relates to novel combinations comprising an NK-1 antagonist  
5 and an agent capable of reducing the pH of gastric juice in the gut. Furthermore, the invention relates to pharmaceutical compositions comprising such combinations and the use of such combinations and compositions in the treatment of diseases related to the gastrointestinal system.

**Background**

10 It is known in the art that proton pump inhibitors and H<sub>2</sub> antagonists may be used to decrease the pH of the gastric juice in the gut. However, neither of these prevent the relaxation of the lower esophageal sphincter. Additionally, prolonged administration of these compounds may be deleterious or give rise to side effects in certain patients. For example, the prolonged administration of a proton pump inhibitor in some cases leads to abdominal pain,  
15 asthenia, constipation, dizziness, or rash.

Substance P is the physiological agent that induces, at least in part, relaxation of the lower esophageal sphincter. NK-1 antagonists are known to block the activity of substance P, thereby blocking the relaxation of the this sphincter. While blocking relaxation of the sphincter can reduce the severity of acid reflux, it does not prevent the aspiration of the acid,  
20 which can lead to gastric asthma.

While various investigators have studied the use of NK-1 antagonists, H<sub>2</sub> antagonists, and proton pump inhibitors independently in such conditions as GERD and gastric asthma, none have proposed the combination therapy provided by the present invention. The present invention relates to a combination of an NK-1 antagonist, an H<sub>2</sub> antagonist, and/or a proton  
25 pump inhibitor that work in concert to provide relief for those who suffer from gastric asthma, GERD, and related conditions.

**Summary of the Invention**

The present invention relates to pharmaceutical compositions, and in particular to pharmaceutical compositions containing a neurokinin-1 (NK-1) antagonist and a proton pump  
30 inhibitor, which are useful in the prevention and treatment of diseases brought about by hypersecretion of gastric acid in the gut and/or relaxation of the lower esophageal sphincter, such as gastric asthma and gastroesophageal reflux disease (GERD). During reflux episodes in

patients with GERD, acid may be aspirated into the lower esophagus, causing esophagitis. GERD or hyper-relaxation of the lower esophageal sphincter can also allow acid to be aspirated into the airways, triggering an asthma attack, also known as gastric asthma.

#### **Detailed Description**

5       The present invention lessens the problems associated with administration of an NK-1 antagonist, an H<sub>2</sub> antagonist, or a proton pump inhibitor alone and/or provides a means for potentially obtaining a therapeutic effect that is significantly greater than that otherwise obtainable with the single agents when administered alone.

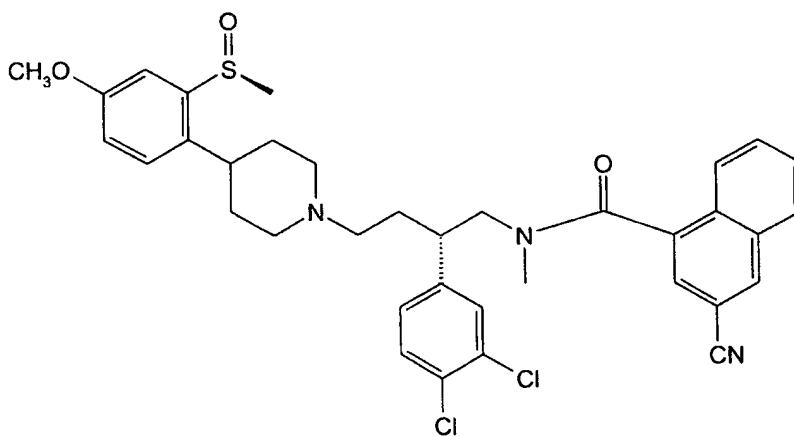
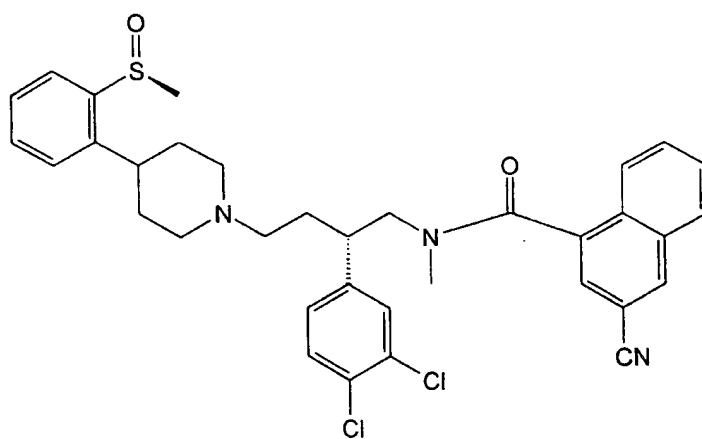
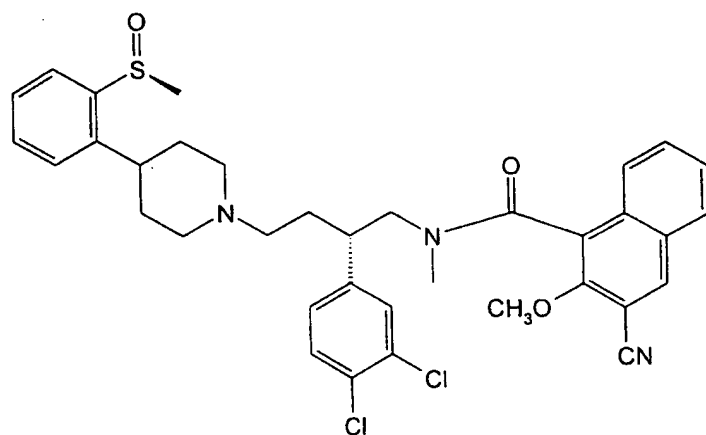
Accordingly, the present invention provides novel combinations, which comprise an  
10 NK-1 antagonist and a proton pump inhibitor; or an NK-1 antagonist and an H<sub>2</sub> antagonist; or an NK-1 antagonist, an H<sub>2</sub> antagonist and a proton pump inhibitor.

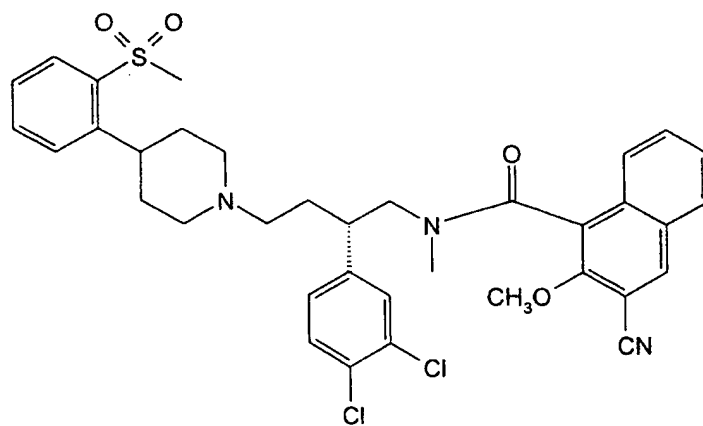
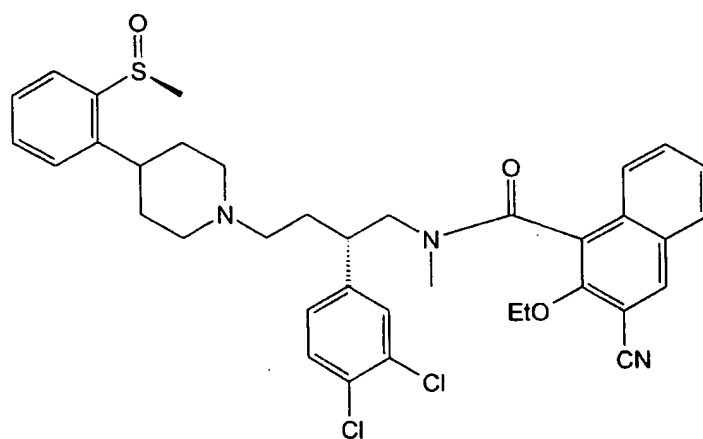
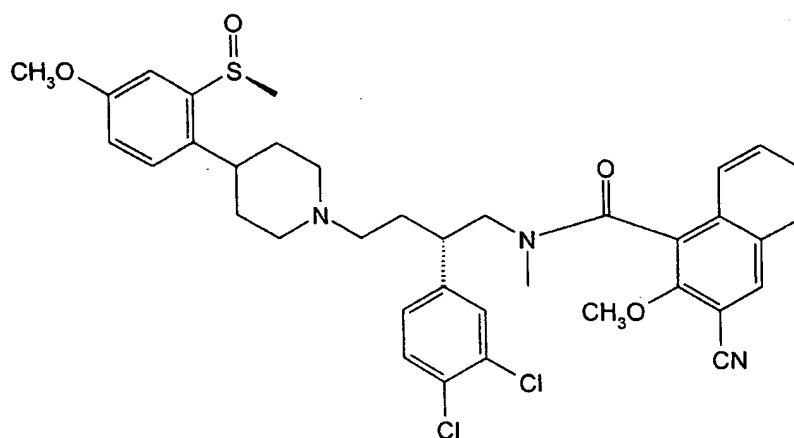
Additionally, the present invention provides pharmaceutical compositions, which comprise an NK-1 antagonist and a proton pump inhibitor; or an NK-1 antagonist and an H<sub>2</sub> antagonist; or an NK-1 antagonist, an H<sub>2</sub> antagonist and a proton pump inhibitor, together  
15 with a pharmaceutically-acceptable carrier and/or diluent.

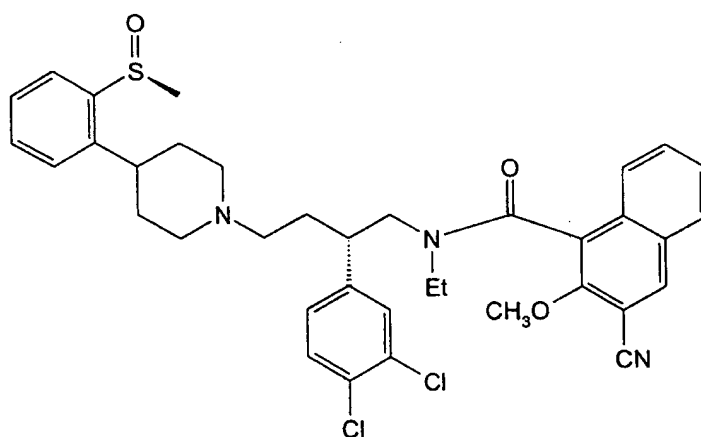
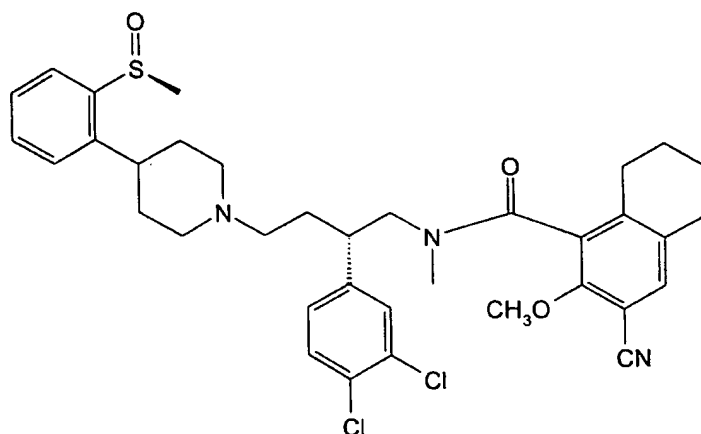
Another aspect of the invention relates to a method for treating disease related to the reflux of gastric acid in the gastrointestinal system, comprising the step of administering a therapeutically-effective amount of the one of the aforementioned combinations.

Another aspect of the invention relates to the use of one of the aforementioned  
20 combinations for the manufacture of a medicament for the treatment of disease related to the reflux of gastric acid in the gastrointestinal system.

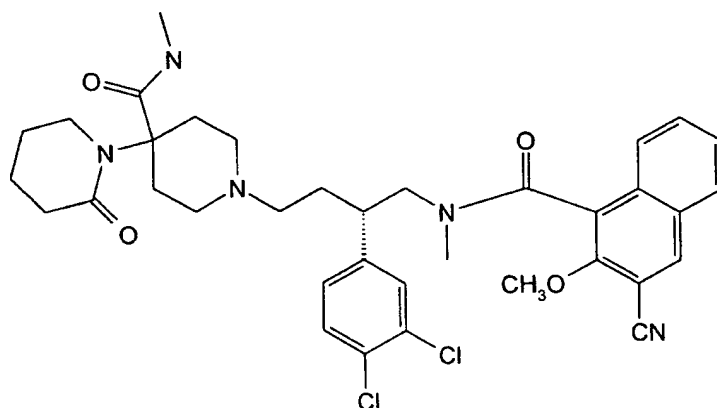
Suitable NK-1 antagonists useful in the compositions of the present invention include any compound capable of acting as an antagonist for the neurokinin-1 receptor, for example, those disclosed in United States Letters Patent Nos. 5,521,199, 5,534,525, 5,567,700,  
25 5,576,333, 5,589,489, 5,602,138, 5,635,509, 5,654,299, 5,710,169, 5,731,309, 5,780,466, 5,576,317 and international applications WO 96/24582, WO 97/19060, WO 98/24447, WO 98/47513, WO 98/04561, WO 96/23787, WO 97/13514, EP 98/0302747 or pharmaceutically acceptable salts thereof. Preferred NK-1 antagonist include, for example:







, and



Other NK-1 antagonists may be identified by the following assays:

#### 5 SP Receptor Binding Assay (Test A)

The ability of a compound of the invention to antagonize the binding of SP at the NK<sub>1</sub> receptor may be demonstrated using an assay using the human NK<sub>1</sub> receptor expressed in Mouse Erythroleukemia (MEL) cells. The human NK<sub>1</sub> receptor was isolated and characterized as described in: B. Hopkins, et al. "Isolation and characterization of the human

lung NK<sub>1</sub> receptor cDNA" Biochem. Biophys. Res. Comm., 1991, 180, 1110-1117; and the NK<sub>1</sub> receptor was expressed in Mouse Erythroleukemia (MEL) cells using a procedure similar to that described in the Neurokinin A (NKA) receptor binding assay below.

**Neurokinin A (NKA) Receptor Binding Assay (Test B)**

5        The ability of a compound of the invention to antagonize the binding of NKA at the NK<sub>2</sub> receptor may be demonstrated using an assay using the human NK<sub>2</sub> receptor expressed in Mouse Erythroleukemia (MEL) cells, as described in: Aharony, D., et al. "Isolation and Pharmacological Characterization of a Hamster Neurokinin A Receptor cDNA" Molecular Pharmacology, 1994, 45, 9-19.

10       The selectivity of a compound for binding at the NK<sub>1</sub> and the NK<sub>2</sub> receptors may be shown by determining its binding at other receptors using standard assays, for example, one using a tritiated derivative of NKB in a tissue preparation selective for NK<sub>3</sub> receptors. In general, the compounds of the invention which were tested demonstrated statistically significant binding activity in Test A and Test B with a K<sub>i</sub> of 1 mM or much less typically  
15 being measured.

**Rabbit Pulmonary Artery: NK<sub>1</sub> in vitro Functional Assay (Test C)**

The ability of a compound of the invention to antagonize the action of the agonist Ac-[Arg<sup>6</sup>, Sar<sup>9</sup>, Met(O<sub>2</sub>)<sup>11</sup>] Substance P (6-11), ASMSP, in a pulmonary tissue may be demonstrated as follows.

20       Male New Zealand white rabbits are euthanized via i.v. injection into the ear vein with 60 mg/kg Nembutal (50 mg/mL). Preceding the Nembutal into the vein is Heparin (1000 units/mL) at 0.0025 mL/kg for anticoagulant purposes. The chest cavity is opened from the top of the rib cage to the sternum and the heart, lungs and part of the trachea are removed. The pulmonary arteries are isolated from the rest of the tissues and cut in half to serve as  
25 pairs.

The segments are suspended between stainless steel stirrups, so as not to remove any of the endothelium, and placed in water-jacketed (37.0 °C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 118.0; KCl, 4.7; CaCl<sub>2</sub>, 1.8; MgCl<sub>2</sub>, 0.54; NaH<sub>2</sub>PO<sub>4</sub>, 1.0; NaHCO<sub>3</sub>, 25.0; glucose, 11.0; indomethacin, 0.005 (to inhibit  
30 cyclooxygenase); and *dl*-Propranolol, 0.001 (to block β receptors); gassed continuously with 95% O<sub>2</sub>-5% CO<sub>2</sub>. Responses are measured on a Grass polygraph via Grass FT-03 transducers.



Initial tension placed on each tissue is 2 grams, which is maintained throughout the 1.0 hour equilibration period. Tissues are washed with the physiological salt solution at 15 minute intervals. At the 30 and 45 minute wash the following treatments are added:  $1 \times 10^{-6}$  M Thiorphan (to block E.C.3.4.24.11),  $3 \times 10^{-8}$  M (S)-N-[2-(3,4-dichlorophenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide (to block NK<sub>2</sub> receptors), and the given concentration of the compound being tested. At the end of the 1.0 h equilibration,  $3 \times 10^{-6}$  M Phenylephrine hydrochloride is added for 1.0 h. At the end of 1.0 h, a dose relaxation curve to ASMSp is done. Each tissue is treated as a individual and is considered finished when it fails to relax further for 2 consecutive doses. When a tissue is complete,  $1 \times 10^{-3}$  M Papaverine is added for maximum relaxation.

Percent inhibition is determined when a tested compound produces a statistically significant ( $p < 0.05$ ) reduction of the total relaxation which is calculated using the total relaxation of the Papaverine as 100%. Potencies of the compounds are determined by calculating the apparent dissociation constants ( $K_B$ ) for each concentration tested using the standard equation:

$$KB = [\text{antagonist}] / (\text{dose ratio} - 1)$$

where dose ratio =  $\text{antilog}[(\text{agonist} - \log \text{molar } EC_{50} \text{ without compound}) - (-\log \text{molar } EC_{50} \text{ with compound})]$ . The  $K_B$  values may be converted to the negative logarithms and expressed as  $-\log \text{molar } KB$  (i.e.  $pK_B$ ). For this evaluation, complete concentration-response curves for agonist obtained in the absence and presence of the compound tested using paired pulmonary artery rings. The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The  $EC_{50}$  values are converted to negative logarithms and expressed as  $-\log \text{molar } EC_{50}$ .

NK-1 antagonists useful in this invention are those that are capable of exhibiting a  $pK_B$  value of greater than 7.0 in the Rabbit Pulmonary Artery Assay described above.

Pharmaceutically-acceptable salts of the NK-1 antagonist, in accordance with the present invention, are the salts with physiologically-acceptable bases and/or acids well known to those skilled in the art of pharmaceutical technique. Suitable salts with physiologically-acceptable bases include, for example, alkali metal and alkaline earth metal salts, such as sodium, potassium, calcium and magnesium salts, and ammonium salts and salts with suitable organic bases, such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine and triethanolamine. Suitable salts with physiologically-acceptable acids include, for

example, salts with inorganic acids such as hydrohalides (especially hydrochlorides or hydrobromides), sulphates and phosphates, and salts with organic acids.

Suitable proton pump inhibitors useful in the compositions of the present invention include any compound known to inhibit the gastric acid pump in the stomach. Examples of  
5 such compounds include omeprazole, S-omeprazole, rabeprazole, lansoprazole, pantoprazole and leminoprazole, or pharmaceutically-acceptable salts thereof. Preferred proton pump inhibitors include omeprazole, (5-methoxy-2-([(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl)-1H-benzimidazole) and S-omeprazole, or pharmaceutically-acceptable salts thereof.

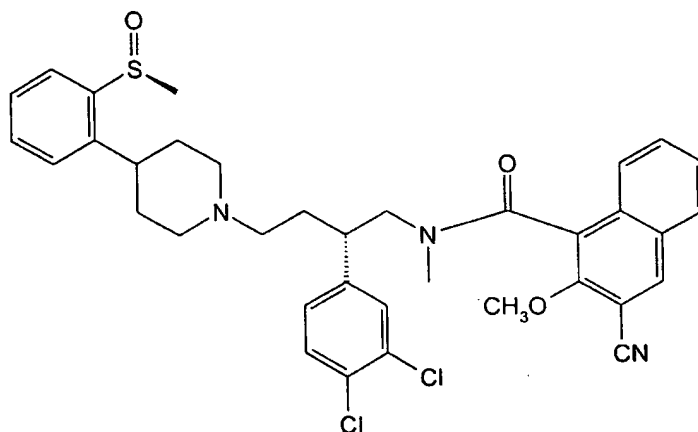
A suitable salt of the proton pump inhibitor omeprazole, or S-omeprazole according to  
10 the invention is an alkaline pharmaceutically-acceptable salt. Examples of such salts include inorganic salts, such as alkali metal salts, e.g., sodium salt, potassium salt, etc., alkaline earth metal salts, e.g., calcium salt, magnesium salt, etc., ammonium salt, organic salts such as organic amine salts, e.g., trimethylamine salt, triethylamine salt, pyridine salt, procaine acid, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methylglucamine  
15 salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, and dibenzylethylenediamine salt.

The proton pump inhibitors used in the present invention are known compounds in the art, and methods for their preparation may be found in the literature. For example, omeprazole is disclosed in EP 5129, lansoprazole in EP 174,726, pantoprazole in EP 166,287,  
20 leminoprazole in GB 2,163,747 and WO 94/27988 describes certain salts of the (-)-enantiomer of omeprazole.

Examples of H<sub>2</sub> antagonists are found in U.S. Patent Nos. 5,889,033, 5,656,652, 5,629,026, 5,622,980, 5,538,737, 5,374,641, 5,273,984, 5,229,418, 5,229,137, 5,221,688, 4,900,741, 4,894,372, 4,847,264, 4,808,589, 4,806,548, 4,788,184, 4,758,576, 4,749,790,  
25 4,738,969, 4,732,980, 4,705,683, 4,694,008, 4,663,331, 4,652,572, 4,636,498, 4,632,927, 4,624,956, 4,622,402, 4,621,142, 4,620,001, 4,608,380, 4,607,107, 4,587,345, 4,574,126, 4,571,398, 4,567,179, 4,567,176, 4,551,466, 4,547,512, 4,540,699, 4,539,316, 4,522,943, 4,503,051, 4,492,794, 4,477,663, 4,466,970, 4,458,077, 4,452,985, 4,450,161, 4,447,611, 4,443,613, 4,439,609, 4,439,437, 4,388,317, 4,385,058, 4,383,115, 4,377,522, 4,359,466,  
30 4,339,439, 4,307,104, 4,279,906, 4,279,819, 4,255,440, 4,230,717, 4,128,658, 4,090,026, however, one of ordinary skill in the art would recognize that other compounds capable of H<sub>2</sub> antagonism would be useful in combination with an NK-1 antagonist.

A preferred pharmaceutical composition of the invention comprises an NK-1 antagonist, or a pharmaceutically-acceptable salt thereof, and a proton pump inhibitor (including any of the proton pump inhibitors specifically named above), together with a pharmaceutically-acceptable carrier and/or diluent.

- 5 An especially preferred pharmaceutical composition of the invention comprises the NK-1 antagonist,



- or a pharmaceutically acceptable salt thereof, and the proton pump inhibitor omeprazole, S-omeprazole, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-  
10 acceptable diluent and/or carrier.

The pharmaceutical compositions of the present invention may be administered in standard manner, for example, by oral or parenteral administration, using conventional systemic dosage forms, such as a tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, or sterile injectable aqueous or oily solutions or suspensions. These  
15 dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like. In particular, compositions for oral administration are preferred.

The doses of an NK-1 antagonist and a proton pump inhibitor which can be administered in accordance with the present invention depends on several factors, for  
20 example, the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen, and the desired result, and additionally the potency of the particular NK-1 antagonist and proton pump inhibitor employed in the composition. In addition, account should be taken of the recommended maximum daily dosages for the proton pump inhibitors.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 1000 mg of an NK-1 antagonists inhibitor and from 1 mg to 80 mg of a proton pump inhibitor. Another embodiment of a dosage formulation will contain 1 to 500 mg of NK-1 antagonist and 1 to 40 mg of a proton pump inhibitor. Another embodiment of a dosage formulation will contain 10 to 400 mg of NK-1 antagonist and 5 to 20 mg of a proton pump inhibitor.

The pharmaceutical compositions of the present invention may be administered up to two times daily and preferably once a day, so that a dose of the NK-1 antagonist in the general range of 1 to 2000 mg/kg, preferably 1 to 1000 mg/kg, more preferably 1 to 500 mg/kg, is administered daily and a dose of proton pump inhibitor in the general range 1 to 40 mg/kg, preferably 1 to 20 mg/kg, more preferably 1 to 10 mg/kg, is administered daily.

The present invention covers the combination of an NK-1 antagonist and a proton pump inhibitor for simultaneous, separate or sequential use in the treatment of complications related to hypersecretion of gastric acid. In one aspect of the present invention, the NK-1 antagonist or a pharmaceutically-acceptable salt thereof and a proton pump inhibitor or a pharmaceutically acceptable salt thereof are presented in admixture in one pharmaceutical dosage form. In another aspect, the present invention covers the administration of separate unit dosages of the NK-1 antagonist and the proton pump inhibitor in order to achieve the desired therapeutic effect. Such separate unit dosages may be administered concurrently or sequentially as determined by the experienced clinician. Preferably the NK-1 antagonists and the proton pump inhibitor are both administered orally.

In another aspect of the invention there is provided a combination of pharmaceutical compositions for combination therapy of selected GERD complications, the combination consisting of pharmaceutical compositions comprising an NK-1 antagonist and a proton pump inhibitor, wherein the selected GERD complications are heartburn and esophagitis.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of gastric ulcer complications.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of gastric asthma complications.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of duodenal ulcer complications.

A further aspect of the present invention comprises the use of an NK-1 antagonist and  
5 a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of pathological hypersecretory complications.

A further aspect of the present invention is a method for treating complications due to hypersecretion of gastric acid wherein a therapeutically-effective amount of an NK-1 antagonist in combination with a proton pump inhibitor is administered systemically, such as  
10 orally or parenterally.

Usually, the proton pump inhibitor will preferably be administered in amounts below that required to cause a reduction in the pH of the contents of the stomach. Where the patient to be treated suffers from pathological hypersecretion, the proton pump inhibitor will preferably be used in greater amounts, e.g. 40 to 100 mg/day. The present invention provides  
15 a novel method for treating hypersecretory complications and the amounts of NK-1 antagonist and proton pump inhibitor required when administered in association with the combined therapy are lower than would normally be used, and thus, any deleterious effects or side effects are minimized.

The effect of a pharmaceutical composition of the present invention may be examined  
20 by using one or more of the published models of hypersecretory complications well known in the art. The pharmaceutical compositions of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, deficits in gastric acid secretion found in hypersecretory patients.

Some of the active compounds, especially some proton pump inhibitors, may be  
25 susceptible to degradation/transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The stability of the active substances may also be affected by moisture, heat, organic solvents and to some degree by light.

In respect to the stability properties of an acid-susceptible proton pump inhibitor, it is  
30 obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of such proton pump inhibitors is best protected from contact with acidic gastric juice by an enteric coating layer. In US-A 4,853,230 such an enteric coated preparation is described. Said preparation contains an alkaline core comprising an acidic susceptible substance, a separating layer and an enteric coating layer. In order to  
5 further enhance the stability during storage the prepared formulation may optionally be packed with a desiccant.

A good mechanical stability can be obtained with an enteric coating layered tablet. WO95/01783 describes such a tablet comprising the acid labile compound omeprazole. However, only an enteric coating layered multiple unit tablet can be made divisible and  
10 dispersible. A further advantage of a multiple unit dosage form is that it disperses into a multitude of small units in the stomach upon administration.

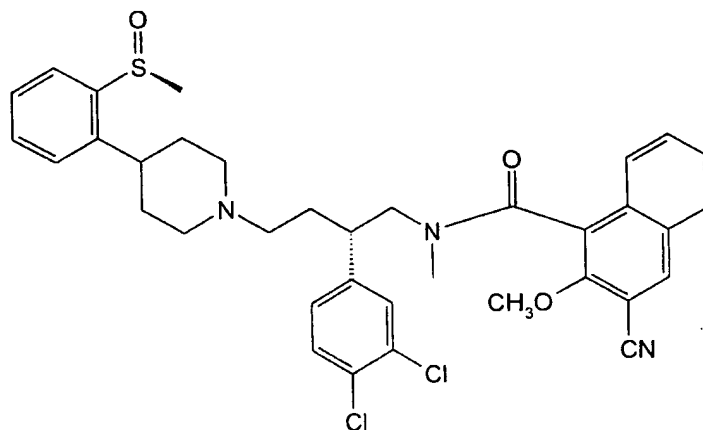
WO 96/01624 discloses tablets comprising enteric coating layered units containing an acid labile proton pump inhibitor or one of its single enantiomers or an alkaline salt thereof can be manufactured by compressing said units into tablets without significantly affecting the  
15 properties of the enteric coating layer.

WO 96/01623 discloses tablets comprising enteric coating layered units containing an acidic susceptible substance in the form of omeprazole or one of its single enantiomers, such as S-omeprazole, or an alkaline salt thereof.

Suitable pharmaceutical formulations for proton pump inhibitors are also described in  
20 US 4,786,505, US 5,817,338, and 5,753,265, hereby incorporated by reference.

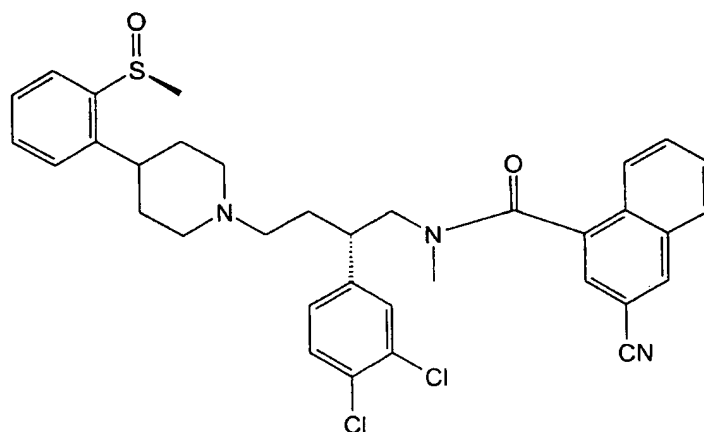
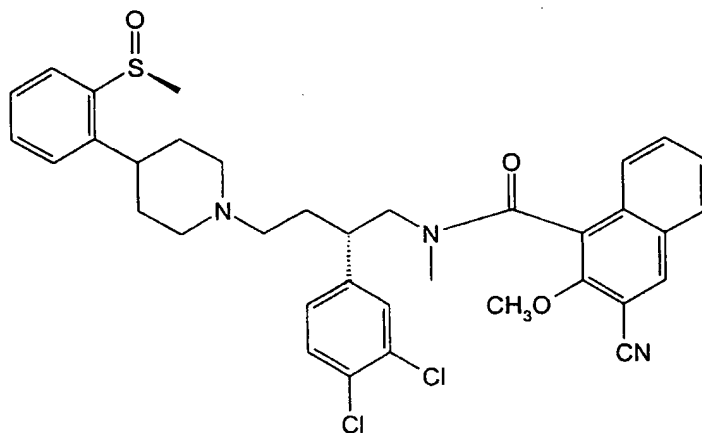
### Example

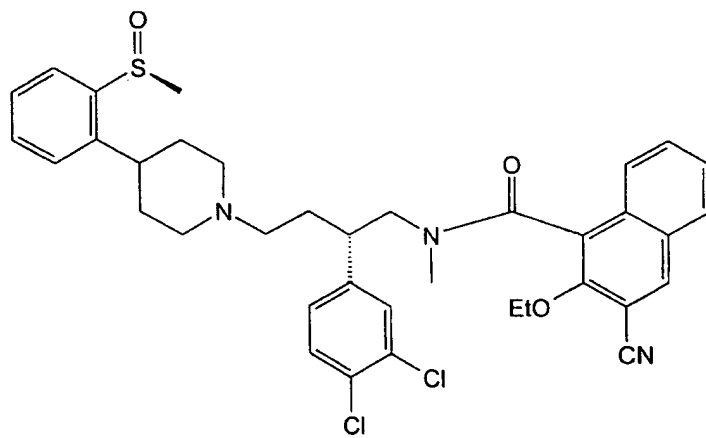
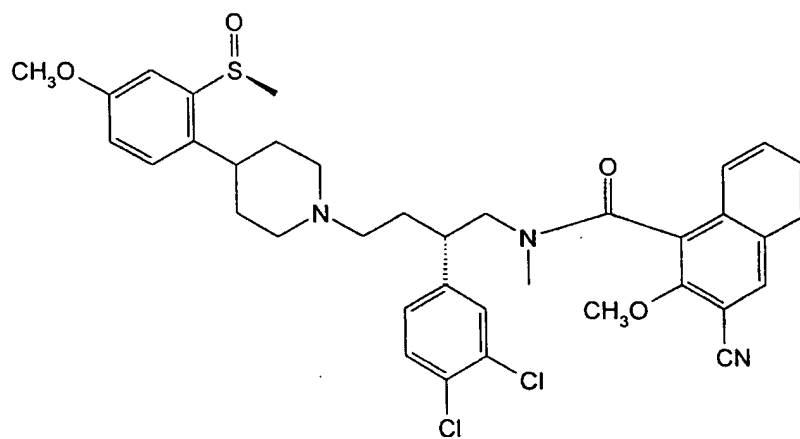
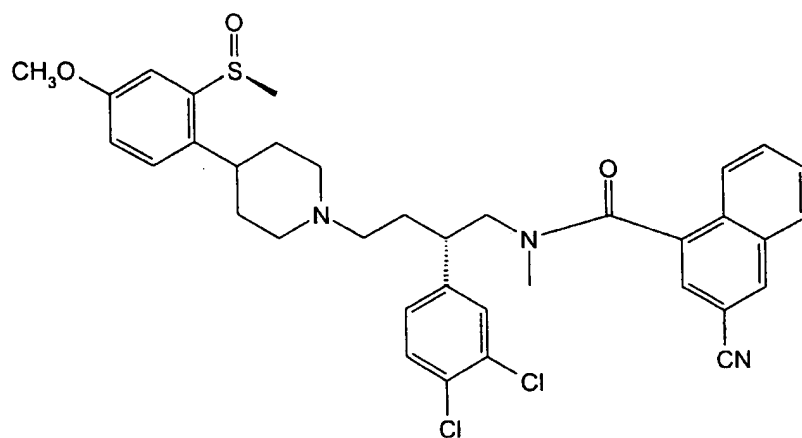
A patient suffering from GERD is treated with a combination of omeprazole (20 mg) Prilosec (tradename) and an NK-1 antagonist (400 mg) having the structure:



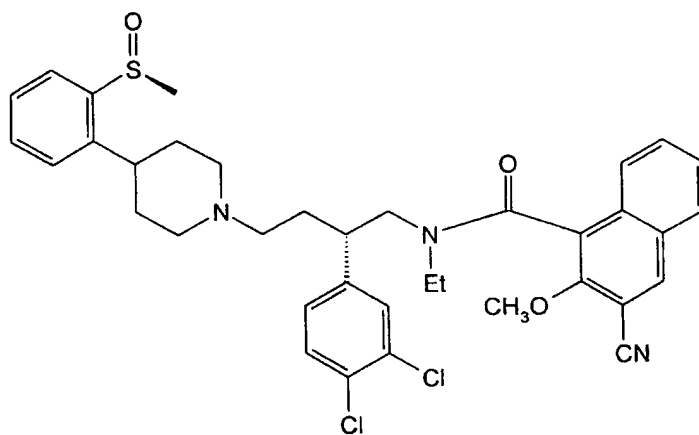
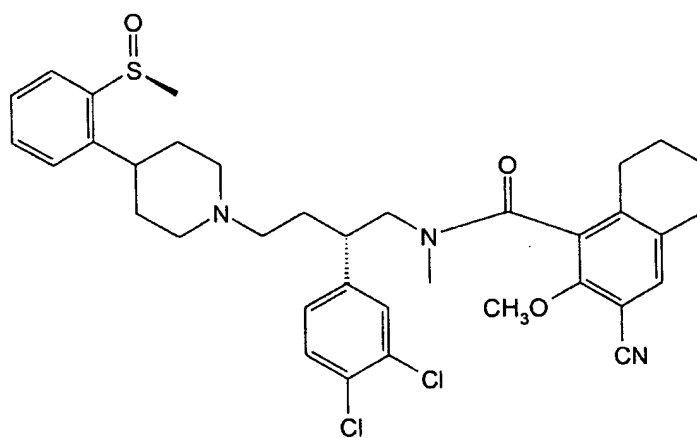
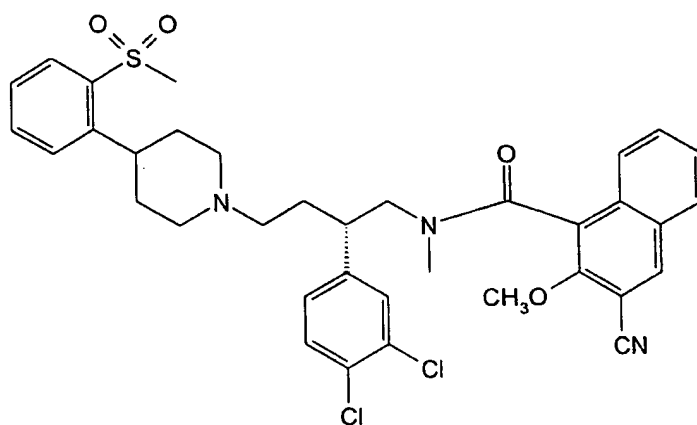
**CLAIMS:**

1. A combination comprising an NK-1 antagonist and an agent capable of reducing the pH of gastric juice in the gut.
- 5 2. The combination according to Claim 1, wherein the agent is a proton pump inhibitor.
3. The combination according to Claim 1, wherein the agent is selected from omeprazole, S-omeprazole, rabeprazole, lansoprazole, pantoprazole and leminoprazole; or a pharmaceutically-acceptable salt thereof.
4. A combination according to Claim 1, wherein the agent is an H<sub>2</sub> antagonist.
- 10 5. A combination according to Claim 1, wherein the NK-1 antagonist is any NK-1 antagonist that is capable of exhibiting a pK<sub>B</sub> value of greater than 7.0 in the Rabbit Pulmonary Artery Assay.
6. A combination according to Claim 1, wherein the NK-1 antagonist is selected from:

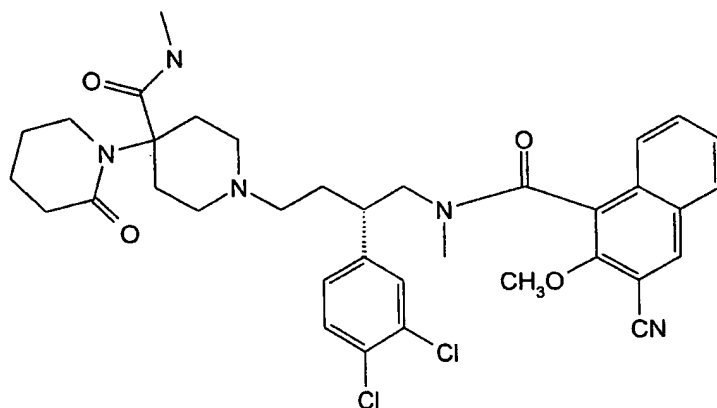








, and



7. A pharmaceutical composition, comprising:  
an NK-1 antagonist;
- 5 an agent capable of reducing the pH of gastric juice in the gut; and  
and a pharmaceutically acceptable carrier or diluent.
8. The pharmaceutical composition according to Claim 7, wherein the agent is a proton  
pump inhibitor.
9. The pharmaceutical composition according to Claim 7, wherein the agent is selected  
10 from omeprazole, S-omeprazole, rabeprazole, lansoprazole, pantoprazole and leminoprazole.
10. A combination according to Claim 7, wherein the agent is an H<sub>2</sub> antagonist.
11. A method for treating disease related to the reflux of gastric acid in the gastrointestinal  
system, comprising the step of administering a therapeutically-effective amount of a  
combination according to any one of Claims 1, 2, 3 or 4.
- 15 12. The method according to Claim 11, wherein the disease is selected from, heartburn,  
esophagitis, gastric ulcer, gastric asthma, duodenal ulcer or pathological hypersecretory  
complications.
13. The use of a combination according to any one of Claims 1 through 4 for the  
manufacture of a medicament for the treatment of disease related to the reflux of gastric acid  
20 in the gastrointestinal system.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 00/01775

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/445 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, WPI Data, PAJ, MEDLINE, CHEM ABS Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Treatment of gastroesophageal reflux disease" THERAPEUTICS LETTER, 'Online! vol. 3, 1994, XP002145877 Retrieved from the Internet: <URL:www.ti.ubc.ca/pages/letter3.html> 'retrieved on 2000-08-25! abstract	1-13
P, Y	HARDING S M: "GASTROESOPHAGEAL REFLUX AND ASTHMA: INSIGHT INTO THE ASSOCIATION" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, US, MOSBY - YEARLY BOOK, INC, vol. 104, no. 2, August 1999 (1999-08), pages 251-259, XP000913686 ISSN: 0091-6749 see conclusion page 255, column 1	1-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search

29 August 2000

Date of mailing of the international search report

13/09/2000

Name and mailing address of the ISA

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Gonzalez Ramon, N

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01775

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STEIN M.R.: "Advances in the approach to gastroesophageal reflux (GER) and asthma." JOURNAL OF ASTHMA, (1999) 36/4 (309-314).  XP000937433 page 311, column 2 -page 312 ----	1-13
A	HALL J.A. ET AL: "Diagnosis and treatment of gastric motility disorders." VETERINARY CLINICS OF NORTH AMERICA - SMALL ANIMAL PRACTICE, (1999) 29/2 (377-395). XP000900801 page 387 -page 391 ----	1-13
T	CROWELL M.D.: "Editorial overview: Neurogastroenterology: Integration of central and peripheral nervous systems in disorders of GI function." CURRENT OPINION IN CENTRAL AND PERIPHERAL NERVOUS SYSTEM INVESTIGATIONAL DRUGS, (2000) 2/3 (326-328). XP000937400 abstract page 327, paragraph 2 ----	1-13
P,Y	US 6 013 680 A (KARIYA KINYA ET AL) 11 January 2000 (2000-01-11) abstract; claims 1,4,5 ----	1-13
P,Y	WO 99 59612 A (APHTON CORP ;GEVAS PHILIP C (US); GRIMES STEPHEN (US); KARR STEPHE) 25 November 1999 (1999-11-25) abstract; claims 4-6,8-10 ----	1-13
P,Y	EP 0 968 720 A (AMANO PHARMA CO LTD) 5 January 2000 (2000-01-05) abstract; claim 3 ----	1-13
A	EP 0 426 479 A (MCNEIL PPC INC) 8 May 1991 (1991-05-08) abstract; claim 3 ----	1-13
A	WO 93 12817 A (WARNER LAMBERT CO) 8 July 1993 (1993-07-08) page 6 -page 7; claims 1,5,8 ----	1-13
E	WO 00 25766 A (ZENECA LTD ;LENGEL DAVID JOHN (US); RUMSEY WILLIAM LEROY (US)) 11 May 2000 (2000-05-11) abstract; claims 6,7 page 5, line 12-30 -----  -/--	1-13

# INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/GB 00/01775

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 00 34243 A (ASTRAZENECA UK LTD ;OHNMACHT CYRUS JOHN (US)) 15 June 2000 (2000-06-15) formula II page 7 page 18, line 18-32 -----</p>	1-13

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13

Present claims 1-13. relate to compounds/compositions defined by reference to desirable characteristics or properties, namely: "a Neurokinin-1 (NK-1) antagonist", "an agent capable of reducing the pH of gastric juice in the gut", "a proton pump inhibitor", "an H2 antagonist".

The claims cover all compounds/compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in the examples and those specifically mentioned in claims 3, 6, 9, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01775

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6013680 A	11-01-2000	JP 11189544 A	13-07-1999
WO 9959612 A	25-11-1999	AU 4079899 A	06-12-1999
EP 0968720 A	05-01-2000	JP 2000026311 A	25-01-2000
EP 0426479 A	08-05-1991	AT 101515 T	15-03-1994
		AU 646230 B	17-02-1994
		AU 6568990 A	09-05-1991
		CA 2028746 A,C	03-05-1991
		DE 69006684 D	24-03-1994
		DE 69006684 T	09-06-1994
		ES 2057439 T	16-10-1994
		GR 90100786 A,B	17-04-1992
		IE 64953 B	20-09-1995
		IN 171746 A	26-12-1992
		JP 3206052 A	09-09-1991
		NZ 235877 A	25-09-1992
		PT 95753 A	30-09-1991
		US 5417980 A	23-05-1995
		US 5204118 A	20-04-1993
		ZA 9008775 A	29-07-1992
WO 9312817 A	08-07-1993	AU 3247593 A	28-07-1993
WO 0025766 A	11-05-2000	NONE	
WO 0034243 A	15-06-2000	NONE	

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